REMARKS

Claims 1-41 are pending in the application.

Claims 1-41 are rejected.

Claims 17 and 18 are original.

Claims 1-16, 19-31, and 37-41 are presently amended to advance prosecution.

Claims 32-36 are cancelled.

Claims 42-46 are newly added.

Applicants request that the above claim set replace the original claim set in the application. No new matter is added.

Discussion of Amendments

As mentioned above, Claims 1-16, 19-31, and 37-41 are presently amended.

Claims 1-16 are amended in the phrases beginning with "optionally" to make the forms singular, change "N-oxyde" to N-oxide," and change "and" to "or." Support for the amendment is found in the instant specification, including page 31 and original Claims 1-16.

Claim 1 is further amended to delete the phrase on page 64, at line 2, to correct the typographical error "remplaced" on page 68, at lines 18 and 22, and to delete the preferred aspects described on page 68, at lines 15, 19-20, 24-25, 25, and 27-28. Support for the amendment is found in the instant specification, including on page 2, at line 17, to page 6, at line 25, and original Claim 1.

Claim 7 is further amended to correct the typographical misspelling "methylen" in the definition of the group Z_1 on page 76, at line 9.

Claims 24 and 25 are amended to state literally what was previously deduced regarding the definition of the groups W, X, etc. Support for the amendment is found in

the instant specification, including page 10, at line 3, to page 12, at line 12, and original Claims 23-25.

Claims 19-30 are amended to replace "Process" with "A process."

Claim 31 is amended to replace "Pharmaceutical" with "A pharmaceutical."

Claim 37 is amended to insert the phrase "having said disease or complaint" after the term "patient." Support for the amendment is found in the instant specification, including page 31, at lines 19-26, and original Claim 37.

Claims 38-41 are amended to correct the typographical misspelling "charactherized."

Claim 38 is further amended to make "cancers" singular. Support for the amendment is found in the instant specification, including page 31, at line 26, and original Claim 38.

New Claims 42-46 are added to claim the subject matter of the preferreds that was deleted from Claim 1, page 68, at lines 15, 19-20, 24-25, 25, and 27-28, as described above.

Claim Rejections - 35 U.S.C. § 112

Claims 37-38 stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly "the specification, while being enabling for the treatment of arthritic diseases, does not reasonably provide enablement for treating all diseases mediated by MMP-13 e.g., all types of cancers, etc."

Applicants respectfully traverse this rejection for the reasons provided below.

(a) The Examiner alleged on page 2 of the Office Action: "... the method of treating covers 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The recitation of 'disease' covers any disease or disorder related to body or mind, and thereby does not limit to the specific diseases which are disclosed in the specification and/or claims."

Applicants respectfully disagree. The method of treating does not cover any disease. It covers diseases currently known to exist and that involve therapy by MMP-13 inhibition. See for example the instant specification on page 1, at line 1, of the instant specification, wherein the invention compounds "are useful . . . for treating complaints involving a therapy with a matrix metalloprotease-13 (MMP-13) inhibitor" (*emphasis added*). See also page 2, at lines 13-15.

Diseases currently known to exist and involve therapy by MMP-13 inhibition are those diseases having pathologies that are currently known to involve a disruption of the equilibrium between MMP-13 activity and matrix remodelling activity in a patient (see page 1, at lines 8-18, and page 1, at line 25, to page 2 at line 2). This disruption can result from a number of different etiologies (e.g., upregulation of MMP-13 activity or down-regulation of TIMP activity or matrix remodelling activity), which are all treatable by therapy involving MMP-13 inhibition.

(b) The Examiner further alleged on page 2 of the Office Action: "The instant claim language covers diseases that are very difficult to treat, e.g., cancer, multiple sclerosis, etc. and diseases that are yet to be discovered, for which there is no enablement provided."

Applicants respectfully disagree with the Examiner's allegation of "no enablement provided." See Applicants' remarks in (a) above in response to the "diseases that are yet to be discovered" part of the Examiner's allegation. Further, MMP-13 inhibition is broadly valuable and useful for treating diseases that are difficult to treat because the pathologies of such diseases intersect at an aspect treatable by a MMP-13

inhibitor. The shared pathological aspect relates to MMP-13 mediated destruction or penetration of a patient's extracellular matrix, which lines joints and blood vessels, comprises myelin surrounding nerve cells, and gives structure to organs. The shared pathological aspect also relates to MMP-13 mediated destruction or penetration of extracellular matrix that leads to tissue inflammation.

An MMP-13 inhibitor would thus treat a variety of diseases, including difficult to treat diseases that may incorrectly seem to the layperson or one of less than ordinary skill in the pharmaceutical art to be wholly unconnected with each other, but which actually commonly involve MMP-13 mediated destruction or penetration of extracellular matrix. For example, such treatment would inhibit MMP-13 mediated metastasis (both by inhibiting initial penetration of blood vessel walls by tumor cells and extravasion of such cells from blood at a removed location) and angiogenesis of any cancer. Such treatment would also inhibit MMP-13 mediated destruction of myelin and inflammation of glia leading to neurological problems such as multiple sclerosis. Such treatment would also inhibit MMP-13 mediated breakdown of the extracellular matrix in heart muscle such as seen in cardiac insufficiency and inhibit atherosclerotic plaque rupture.

Applicants have presented positive MMP-13 inhibitory data in Table 1 on page 63 of the instant specification. It is well established that allegations of plausible utilities are sufficient to satisfy the law and that any combination of in vitro or in vivo testing can be sufficient to establish the credibility of the asserted utility (see MPEP 2164.02 under the heading "CORRELATION:*IN VITRO/IN VIVO*"). A rigorous or an invariable exact correlation between in vitro data and in vivo efficacy is not required (see MPEP 2164.02). In the instant application, the data of Table 1 in view of the knowledge of the artisan of ordinary skill in the pharmaceutical art are sufficient to establish the plausibility of the utilities of instant Claims 37-38.

(c) Applicants have identified a selective series of MMP-13 inhibitors (see the instant specification on page 32, at lines 14-18), something that the Examiner alleged on page 3 of the Office Action to be difficult.

(d) The Examiner further alleged on pages 4-6 of the Office Action: "…. There is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders embraced the instant claims. Many of the claimed disorders, e.g., cancer, etc., have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the claimed compounds can treat the different types of diseases recited in the claim having diverse mechanisms" (p. 4).

Applicants respectfully disagree. For the reasons provided in (b) above, such inhibition will benefit patients suffering from a variety of different diseases or complaints because the involvement of destruction of extracellular matrix is common to these diseases or complaints. As shown above, Applicants method of treating does not involve a different mechanism of action for each different disease or complaint, but a single common therapy of MMP-13 inhibition. Thus, the Examiner's argument is rendered moot on this point. Further, Applicants believe that one of ordinary skill in the pharmaceutical art would know that aspects of the pathologies of the diseases recited in the instant specification, for example on page 2, at lines 3-9, relate to MMP-13 activity.

Applicants admit that they have not presented clinical data to show the therapeutic effect of the instant methods of treating. In this regard, Applicants are reminded of the situation the court addressed in In re Brana, 34 USPQ2d 1437 (CAFC 1995), where the court said:

> "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas . . . ". (34 USPQ2d at 1442-1443).

Clinical data in humans is thus not required to establish plausible utility under patent law.

Instead, Applicants have presented in vitro data, which for the reasons provided in above, are sufficient to establish the utilities in view of the state of the art of MMP-13 and diseases (see MPEP 2164.02, *supra*, and In re Brana, *supra*). Applicants deem that the involvement of MMP-13 activity in the diseases or complaints recited in the art or in Claims 37-38, combined with Applicants in vitro data are sufficient to establish plausible utilities for the instant invention compounds (see MPEP 2164.03).

In summary and with further respect to the Examiners points 1) to 7) on pages 5-6 of the Office Action:

(1) Applicants diverse list of diseases does not destroy enablement because MMP-13 inhibition is a common therapeutic effect that is useful for treating each of these diseases.

(2) The Examiner's characterization of treating the diverse diseases by multiple mechanisms does not apply, and thus the allegation that there is no known single group of compounds of similar structure that have been demonstrated to treat a wide variety of diseases is moot.

(3) Applicants have demonstrated sufficient predictability under patent law by their presentation of the in vitro data in specification in view of the well known state of the MMP-13 art. Clinical trials or animal in vivo data are not required in the MMP-13 pharmaceutical art to satisfy plausible utility requirements under patent law, and the application by the Examiner of a substantially higher standard of predictability such as that which would satisfy a regulatory agency such as the U.S. Food and Drug Administration is not proper. The undue experimentation that the Examiner alleges is directed towards clinical trials in humans, something that the court in In re Brana, supra, has said is not required to establish utility under patent law.

(4) and (5) At least 27 working examples are disclosed in the instant specification. It is not necessary to provide dosages in view of Applicants disclosure and the level of skill in the pharmaceutical art (MPEP 2164.01(c)).

(6) As mentioned above, the scope of Claims 37-38 is limited to treating diseases currently known to involve therapy with an MMP-13 inhibitor.

(7) Applicants disclosure of Example 28 provides a ready and simple method for one of ordinary skill in the pharmaceutical art to ascertain in vitro MMP-13 inhibitory activity of an invention compound, and thus determine plausible utility under patent law for method of treating of Claims 37-38.

In view of the above remarks, Applicants deem Claims 37-38 are enabled and that rejection of Claims 37-38 under 35 U.S.C. § 112, first paragraph, is overcome.

Claim Rejections - 35 U.S.C. § 112

Claims 1-41 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

Applicants respectfully traverse this rejection for the reasons provided below. Applicants refer to their above remarks under *Discussion of Amendments*.

Regarding the Examiner's reason 1., the objected to phrase "The invention relates to cyclized quinazolines of formula (I)" has been deleted.

Regarding the Examiner's reason 2., Applicants have retained the term "optionally" in Claims 1-16 and respectfully ask the Examiner to reconsider the request for their deletion. The deletion of "optionally," which the Examiner considers redundant, could be erroneously misinterpreted by a court in any future proceeding as a narrowing amendment that creates prosecution history estoppel. (see, *inter alia*, Festo Corp. v. Shoketsu Kinoku Kogyo Kabushiki Co., Ltd., 122 S.Ct. 1831, 62 USPQ2d 1705 (2002)) Deletion of optionally could thus lead a court to erroneously limit the scope of Applicants' claims in which the term appears. Further, Applicants submit that use of the term "optionally" does not render the claim indefinite or otherwise unpatentable under 35 U.S.C. § 112, second paragraph.

On the other hand, Applicants have complied with the Examiner's request to replace the "plurality of the terms, e.g., 'forms' ..." with corresponding singular terms and replace "and" with "or" to place the language in more conventional Markush form.

Regarding the Examiner's reason 3., Applicants respectfully traverse the Examiner's assertion that what is intended by the original term "isomers" in instant Claim 1 and Claims 2-15 dependent therefrom is not clear. Applicants deem that one of ordinary skill in the pharmaceutical art would know that the term "isomers" literally embraces stereoisomers, including cis/trans, syn/anti, (E)/(Z), (R)/(S), diastereomers, enantiomers, and the like. For example, R_2 in Claim 1 may be $(C_1\text{-}C_6)$alkyl (page 64, line 17) and $(C_1\text{-}C_6)$alkyl may be branched (page 27, at line 8). Thus R_2 includes the group -$C(H)(CH_3)CH_2CH_3$, which group possess a chiral carbon. In a further example, the group R_3 in Claim 1 may be a $(C_2\text{-}C_6)$alkenyl (page 66, line 16), including the group -$C(H)=C(H)CH_3$, which group may be cis or trans, (E) or (Z). In a further example, the group X in Claim 1 may be a cycloalkyl of 3 to 8 carbon atoms substituted by OH. Such a group X includes a 2-hydroxycyclohexyl, which may be cis or trans, syn or anti.

Conversely, structural or positional isomers are not literally embraced by instant Claims 1-16. The skilled artisan would thus not read the term "isomers" on structural or positional isomers. Accordingly, one of ordinary skill in the pharmaceutical art would clearly know that the original term "isomers" means stereoisomers, but not structural or positional isomers.

Regarding the Examiner's reason 4., Applicants have amended Claim 1 as described above to delete the preferreds and have added new claims directed to the preferreds.

Regarding the Examiner's reason 5., the typographical error "remplaced" has been replaced with the correct term "replaced."

Regarding the Examiner's reason 6., the "N-oxyde" spelling has been replaced with a more common English spelling, "N-oxide."

Regarding the Examiner's reason 7., the phrase "as defined above" has been replaced with the phrase "as defined in Claim 23."

Regarding the Examiner's reason 8., Claims 32-36 are cancelled, rendering the rejection with respect to these claims moot.

Regarding the Examiner's reason 9., Applicants respectfully traverse the Examiner's allegation that the term "complaint" in Claims 37 and 38 is not a proper term. The term "complaint" is found in Webster's New Collegiate Dictionary (1975) in 2b as "a bodily ailment or disease." For analogous reasons related to the term "optionally" above, deletion of "complaint" would trigger prosecution history estoppel under Festo, *supra*. Accordingly, Applicants have left the term in the claims and respectfully request reconsideration of the request to delete the term complaint.

On the other hand, Applicants have amended Claims 37 and 38 by inserting the phrase "having said disease or complaint" and by replacing "cancers" with "cancer."

In view of the above amendment and remarks, Applicants deem Claims 1-41 are definite and patentable under 35 U.S.C. § 112, second paragraph, and deem that the rejection of Claims 1-41 under 35 U.S.C. § 112, second paragraph, is overcome.

Claim Rejections - 35 U.S.C. § 101

Claims 32-36 stand rejected under 35 U.S.C. § 101 as allegedly not being proper process claims.

Claims 32-36 are cancelled, rendering their rejection moot.

Claim Rejections - 35 U.S.C. § 102

Claims 1-20 and 31-41 are rejected under 35 U.S.C. § 102(e) as allegedly "being anticipated by Andrianjara et al., U.S. Patent Application Publication 2003/0078276 (filed February 13, 2002)."

Applicants respectfully traverse the rejection for the reasons provided below.

Applicants enclose herewith a "Declaration Under 37 C.F.R. § 1.131 Of Prior Invention" and a copy of WO 02/064595 cited therein. As shown by the declaration in view of WO 02/064595, the Applicants invented the subject matter of the instant application, 10/075,654, prior to February 13, 2002. February 13, 2002, is the effective 102(e) date for the subject matter of 2003/0078276 upon which the instant rejection is based.

Accordingly, Applicants deem Claims 1-20 and 31-41 are not anticipated by U.S. Patent Application Publication 2003/0078276 and thus their rejection under 35 U.S.C. § 102(e) is overcome.

Domestic Priority

Applicants note with pleasure the Examiner's acknowledgement of their instant claim for domestic priority to U.S. provisional patent application number 60/268,757, filed February 14, 2001.

Supplemental Information Disclosure Statement

Applicants herein make available to the Patent and Trademark Office a supplemental Form PTO-1449 enclosed herewith, which cites WO 00/09485, WO 01/12611, WO 02/34726, WO 02/34753, EP 0,935,963, EP 1,138,680, WO 02/064080, and WO 02/064595.

The Examiner is respectfully requested to consider carefully the complete text of these cited references in connection with the examination of the above-identified application in accord with 37 CFR §1.104(a).

It is respectfully requested that all references considered by the Examiner, including but not limited to those cited in the enclosed supplemental IDS, be listed in the "References Cited" portion of any patent issuing from the instant application (MPEP § 1302.12).

Conclusion

In view of the amendment to Claims 1-16, 19-31, and 37-41, cancellation of Claims 32-36, and above remarks, Applicants deem that the rejection(s) of Claims 1-41 have been overcome and that the application is in condition for allowance. Applicants respectfully request prompt consideration of the now pending claims and newly cited art, and allowance of patentable Claims 1-31 and 37-41.

The Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment, to deposit account number 23-0455.

The undersigned would welcome a telephone call from the Examiner to discuss any matters related to this case that the Examiner thinks are conducive to telephonic resolution.

Respectfully submitted,

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References cited in Form PTO-1449